Regulatory Strategy for the Further Implementation and Enforcement of the Dietary Supplement Health and Education Act of 1994

This regulatory strategy is organized into three sections: (1) Monitoring and evaluation of product and ingredient safety, (2) assurance of product quality (current good manufacturing practice (CGMP) regulations), and (3) monitoring and evaluation of product labeling.

I. Monitoring and Evaluation of Product and Ingredient Safety

A. General Information

The Federal Food, Drug, and Cosmetic Act (the act) prohibits the distribution of adulterated foods in interstate commerce. Under section 402(f)(1)(A) of the act (21 U.S.C. 342(f)(1)(A)), a food is considered adulterated if, among other things, it is a dietary supplement or contains a dietary ingredient that presents a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use. FDA bears the burden of establishing that the product presents a significant or unreasonable risk. Because dietary supplements are presumed to be safe, FDA's evaluation of whether a dietary supplement presents a significant or unreasonable risk generally takes place after the product is already on the market, with the exception of products that contain certain new dietary ingredients (NDIs), as discussed in this document. In the **Federal Register** of February 11, 2004 (69 FR 6788), FDA interpreted and

applied the ‘‘unreasonable risk’’ standard in a final rule declaring dietary supplements containing ephedrine alkaloids adulterated because they present an unreasonable risk of illness or injury. As that rule explains, ‘‘unreasonable risk’’ implies a risk-benefit calculation that weighs a product’s risks against its benefits under the conditions of use recommended or suggested in the product’s labeling or, if the labeling is silent, under ordinary conditions of use. The Secretary of Health and Human Services also has authority under the statute to act where a product poses an ‘‘imminent hazard’’ to public health and in certain other situations, such as when a product is contaminated with filth.

The act requires a premarket safety notification for certain NDIs introduced into commerce following the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under section 413(c) of the act (21 U.S.C. 350b(c)), an ‘‘NDI’’ is a dietary ingredient that was not marketed in the United States before October 15, 1994. A dietary supplement that contains an NDI is deemed to be adulterated unless one of two conditions is met; either: (1) The dietary supplement must contain only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered or (2) there must be a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe, and the manufacturer or distributor of the dietary supplement containing the NDI must provide FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing

such dietary ingredient will reasonably be expected to be safe.

This notification is to be provided at least 75 days before the product is introduced or delivered for introduction into interstate commerce. If a dietary supplement containing an NDI is subject to the notification requirement and this requirement is not met, or if there is no history of use or other evidence of safety establishing a reasonable expectation of safety, the dietary supplement is deemed to be adulterated under section 402(f)(1)(B) of the act because there is inadequate information to provide reasonable assurance that the product does not present a significant or unreasonable risk of illness of injury. DSHEA established the premarket notification process for NDIs that have not been present in the food supply as articles used for food without chemical alteration, placing upon the manufacturer or distributor the premarket responsibility for providing to FDA the basis upon which the firm has concluded that the NDI is reasonably expected to be safe.

FDA is concerned that many products currently available to consumers may contain NDIs for which required NDI notifications have not been submitted or for which the information submitted in the notification or otherwise available does not establish a reasonable expectation of safety. FDA intends to use the authority of the NDI provisions of the act to consider: Whether there are valid and reliable data establishing that the NDI is reasonably expected to be safe; whether products currently on the market were required to, but did not, submit an NDI notification; and whether products on the market contain NDIs that lack a reasonable expectation of safety and for which FDA previously raised safety concerns when premarket notifications for these ingredients were submitted.

B. Strategies

1. ‘‘Old’’ Dietary Ingredients (i.e., Dietary Ingredients First Marketed in the United States Before October 15, 1994)

FDA is taking steps to ensure that these ingredients, and dietary supplements containing these ingredients, do not pose a significant or unreasonable risk to consumers.

First, the agency plans to improve the evidentiary base for safety and enforcement decisionmaking through external collaborations and internal resource priority-setting. CFSAN has developed intramural and extramural research and scientific review collaborations with the National Institutes of Health (NIH) Office of Dietary Supplements and National Center for Complementary and Alternative Medicine, the National Toxicology Program in the Department of Health and Human Services, the University of Mississippi’s National Center for Natural Products Research, FDA’s National Center for Toxicology Research, and the Association of Analytical Chemists. Several years ago, FDA contracted with the Institute of Medicine and the National Research Council of the National Academies for a report on a framework for evaluating the safety of dietary supplements. This report (Ref. 1) was issued in April 2004.

Second, FDA intends to implement a transparent and systematic process for evaluating safety concerns about dietary ingredients and dietary supplements. The process begins with ‘‘signal detection.’’ Signals of a possible safety concern may derive from a variety of sources, including Federal, State, and local counterparts; adverse event reports; foreign regulatory actions; media

reports; information from consumer groups; and consultation with experts. FDA will determine when the quality or quantity of these signals raises a reasonable concern that health problems may result from ingestion of a dietary ingredient or dietary supplement. FDA may then seek an independent expert third party review and evaluation of the risks and benefits of the ingredient or supplement. FDA intends to consider any independent report and other evidence as appropriate, to determine whether there exists an adequate basis for a finding of significant or unreasonable risk, or whether additional research, labeling or outreach efforts are needed. Regulatory actions will be based upon the totality of the scientific evidence available, including the pharmacology of the substance, scientific literature, adverse event reports, and evidence-based reviews.

Third, the agency plans to use its Web site (*http://www.fda.gov*) as an information resource for consumers. FDA also intends to conduct other outreach efforts to give consumers access to reliable scientific information about the safety of specific dietary ingredients and dietary supplements. The purpose of these efforts is to provide information for consumers so that they may make more informed choices. Prototypes of science-based summaries called ''Consumer Highlights'' were presented in a poster session at the FDA Science Forum in 2004.

Fourth, the agency intends to educate consumers and health care providers on how to report to FDA adverse events or other product complaints via the existing MedWatch reporting system, including what types of information are critical to allow for further evaluation and followup.

Fifth, the agency plans to encourage manufacturers, marketers, and

distributors of dietary supplements to report to FDA adverse events associated with use of their products.

2. NDIs (i.e., Dietary Ingredients Not Marketed in the United States Before October 15, 1994).

FDA is taking three steps to ensure that dietary supplements that contain NDIs are not adulterated under sections 402(f)(1)(B) and 413(a) of the act.

First, FDA intends to convene a public meeting to obtain comment on issues pertaining to NDIs. The meeting announcement, which was published in the **Federal Register** on October l, 2004 (69 FR l), outlines the key areas upon which FDA is seeking public comment. These include, among other topics, the following: the meaning and scope of dietary ingredient categories listed in section 201(ff)(1) of the act (21 U.S.C. 321(ff)(1)); what types of chemical alteration or other processing, if any, should be considered to result in an NDI when an old dietary ingredient is modified in some way (The Institute of Medicine, in its report (Ref. 1), recommended that when the formulation or processing of a dietary ingredient is changed, it should be considered an NDI within the meaning of DSHEA); and what information about history of use or other evidence of safety is sufficient to establish that a dietary supplement containing an NDI will reasonably be expected to be safe.

Second, FDA plans to bring enforcement actions against marketed dietary supplements that contain NDIs for which a required notification has not been submitted.

Third, FDA plans to bring enforcement actions against marketed dietary supplements that are adulterated under sections 402(f)(1)(B) and 413(a) of the

act because they contain an NDI for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.

II. Assurance of Product Quality; CGMP

A. General Information

DSHEA gives FDA the authority to issue dietary supplement CGMP regulations. These regulations will help ensure that dietary supplements (and dietary ingredients) are of high quality, do not contain contaminants or impurities, and are labeled to accurately reflect the ingredients in the product.

FDA published a proposed rule on CGMP for dietary supplements in the **Federal Register** of March 13, 2003 (68 FR 12158). Examples of product quality problems the proposed dietary supplement CGMP regulations would help prevent include superpotent and subpotent products, wrong ingredients, presence of contaminants (e.g., bacteria, pesticide, glass, and lead), underfilled containers, foreign material in a dietary supplement container, improper packaging, and mislabeling. The 90-day public comment period on the proposed rule was extended 60 days, and closed on August 11, 2003. During the comment period, FDA staff participated in two outreach meetings and an FDA-sponsored satellite downlink, as well as three outreach meetings organized by industry groups to ensure that dietary supplement manufacturers (especially small manufacturers) and other interested parties were familiar with the proposal.

FDA received more than 1,600 pages of comments that are now being evaluated. Publication of a CGMP final rule is one of the agency's highest

priorities.

B. Strategies

FDA is taking three steps to help ensure that dietary supplements are manufactured, packaged, labeled, and held in a manner that will prevent them from being adulterated under the act.

First, FDA is working to publish a final rule on dietary supplement CGMP.

Second, FDA is developing a plan for outreach and implementation of the final rule on dietary supplement CGMP. The plan will contain the following two elements: (1) Communication mechanisms (e.g., outreach meetings, information kits, and website communications, including satellite training sessions) to disseminate dietary supplement CGMP information to the general public, FDA field offices, health care professionals, and industry; and (2) inspection and enforcement mechanisms to ensure that dietary supplement manufacturers comply with the CGMP final rule.

Third, FDA will incorporate the CGMP requirements in the final rule into a compliance program to ensure that the agency has an effective, active inspection and compliance program for dietary supplement CGMP. As part of that program, FDA intends to evaluate the conditions and practices under which dietary supplements are manufactured, packaged, labeled, and held in dietary supplement firms and monitor the quality of finished dietary supplements through postmarket surveillance activities such as sampling and analyzing dietary supplement products in distribution.

III. Monitoring and Evaluation of Product Labeling

A. General Information

Under section 201(k) of the act (21 U.S.C. 321 (k)), the term ‘‘label’’ means a display of written, printed, or graphic matter upon the immediate container of any article. Section 201(m) of the act defines the broader term ‘‘labeling’’ to include all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.

The act and its implementing regulations govern words, statements, and other information that must or may appear on the label, and provide that any required label information must also appear on or be visible through any outside retail packaging (e.g., a cardboard box that holds single-serving packs of a product).

FDA regulates dietary supplement labeling, including labeling claims, package inserts, and accompanying literature such as flyers, brochures, and catalogs. The Federal Trade Commission (FTC) regulates dietary supplement advertising.

Dietary supplements must be labeled as such using the term ‘‘dietary supplement’’ or another appropriately descriptive term that includes the word ‘‘supplement.’’ Dietary supplement labels must also bear a supplement facts panel that identifies each dietary ingredient and the amount of it contained in each serving of the product, as well as a list of any ingredients not identified in the supplement facts panel. The nutrition labeling regulations specify the criteria FDA will apply to determine whether a deviation from the declared amount of a dietary

ingredient in a dietary supplement will cause it to be misbranded.

The act, as amended by DSHEA, provides for the use of claims about the effects of a dietary supplement on the structure or function of the body, claims of general well-being from consumption of a dietary ingredient, and claims of benefits related to classical nutrient deficiency diseases (see 21 U.S.C. 343(r)(6)). Such claims may appear in dietary supplement labeling without premarket review or authorization from FDA. However, claims may not be made about the use of a dietary supplement to diagnose, prevent, mitigate, treat, or cure any nonnutrient deficiency disease (unless authorized under the drug or health claim provisions of the act; the latter comprehend only risk reduction claims). Structure/function claims, claims of general well-being, and claims about classical nutrient deficiency diseases require notification to FDA within 30 days of marketing and must be accompanied by the following disclaimer: ''This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.'' In addition, the manufacturer must have substantiation that the claim is truthful and nonmisleading.

As with conventional foods, authorized nutrient content claims and health claims may be made in dietary supplement labeling if the product qualifies to bear the claim. Nutrient content claims characterize the level of a nutrient in a food. Health claims describe the role of a food substance in reducing the risk of a disease. Claims that a dietary supplement is useful in diagnosing, mitigating, treating or curing a specific disease or class of diseases are not considered health claims. Products sold as dietary supplements that bear such disease claims are subject to regulation as drugs.

FDA is concerned about disease claims for dietary supplements because such claims may encourage consumers to self-treat for a serious disease without benefit of a medical diagnosis or treatment; may cause consumers to substitute potentially ineffective products for proven ones, foregoing or delaying effective treatment for serious and life-threatening illnesses; and may encourage consumers to feel sufficiently protected from developing serious diseases that they delay or forego regular screening, and thereby forfeit the opportunity for early medical treatment that may be critical to survival. The use of dietary supplements to treat disease may also increase the risk of adverse reactions due to the interaction of the dietary supplement with other compounds a consumer may be taking for that disease or for other conditions.

FDA is also concerned about unsubstantiated structure/function claims. FDA recognizes that the claims provisions of DSHEA were enacted, in part, to promote consumer access to legal, properly labeled dietary supplements. The use of unsubstantiated structure/function claims is not only unlawful but leads many consumers to buy fraudulent dietary supplements that do not do what they are purported to do. Whether consumers are purchasing dietary supplements to improve their appearance, promote general health, or help them maintain a healthier lifestyle, consumers can fall victim to products that cheat them out of their money and steer them away from products that are proven to achieve the results they are seeking. Like dietary supplements whose labeling bears illegal disease treatment claims, dietary supplements that bear unsubstantiated structure/function claims in their labeling may present specific dangers such as encouraging consumers to substitute them for products or health promotion

strategies whose benefits are backed up by scientifically accurate information. For example, weight loss products that are promoted using claims that consumers can lose weight without changing their diet or physical activity do not help consumers lose weight and leave them at greater risk of health problems associated with overweight, such as insulin resistance and heart disease. Unsubstantiated claims may also encourage consumers to use dietary supplements for conditions that, while not diseases themselves, may indicate a possibility that a consumer has a disease or is at risk for a disease and should seek the advice of a health care provider. For example, a product may be falsely promoted as being able to benefit elderly men with certain urinary conditions that may also be symptoms of serious prostate disorders in need of early diagnosis, such as prostate cancer. Finally, products bearing unsubstantiated claims also cause consumers economic loss and undermine the goals of FDA's health information initiative to get consumers better product information so that they can make informed choices.

B. Strategies

FDA will continue to take appropriate action against products whose labeling violates the act. FDA enforces its labeling regulations, in part, by conducting inspections and collecting samples as part of its Dietary Supplement Compliance Program (see Compliance Program 7321.008, *http://www.cfsan.fda.gov/~comm/cp21008.html*) and investigating complaints to the agency.

FDA will continue to work closely with the FTC to coordinate FDA's regulatory oversight of claims on product labeling and FTC's regulatory oversight

of advertising claims. For example, FDA participates in ''Operation Cure-All.'' This cooperative effort dates back to 1997, when FTC, FDA, Health Canada, and various State Attorneys General began a law enforcement and consumer education campaign against the fraudulent marketing of dietary supplements and other health products on the Internet. The agencies have since moved to stop Internet scams for products purporting to cure cancer, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), and other life-threatening diseases. In addition, FDA has sponsored a National Health Fraud Working Group since 1992. This group comprises representatives from the Association of Food and Drug officials, State Attorneys General, FTC, Health Canada, Mexico, and FDA. It meets on a regular basis to promote coordinated regulatory activities and information exchange.

FDA intends to undertake five actions to help ensure that dietary supplement labeling is truthful and nonmisleading. First, the agency will continue to identify and take action against dietary supplements making claims that are not supported by scientific evidence. Significant progress has been made under the Dietary Supplement Enforcement Plan announced in December 2002 (*http://www.fda.gov/oc/mcclellan/chbn.html*). This plan is routinely re-assessed to ensure optimal utilization of resources.

Second, FDA intends to develop and publish a draft guidance addressing what constitutes adequate scientific substantiation for structure/function claims and claims of a benefit related to a nutrient deficiency disease. This guidance document is intended to describe the amount, type, and quality of evidence a manufacturer should have to substantiate claims of these types. FTC has typically

applied a substantiation standard of ‘‘competent and reliable scientific evidence’’ FDA intends to apply this standard also.

Third, FDA plans to identify and take enforcement action against products whose labeling fails to reveal material facts, targeting those products that pose the greatest risks to consumers. Under sections 201(n) and 403(a)(1) of the act (21 U.S.C. 343(a)(1)), a dietary supplement is misbranded if its labeling omits information that is material in light of the claims made for the product or the consequences that may result from using the product. Situations in which a product could be misbranded for omitting a material fact include, for example, failure to disclose known drug interactions, adverse effects, contraindications, or other information necessary for consumers to safely use the product or understand its labeling.

Fourth, FDA intends to obtain and analyze samples of dietary supplements in the marketplace to verify that the contents are consistent with the labeling.

Fifth, as a routine part of FDA’s surveillance, investigative and other regulatory activities, the agency will review Supplement Facts panels to determine whether the substances listed as dietary ingredients can be lawfully marketed in dietary supplements. For example, dietary supplements that contain ephedrine alkaloids from a botanical source are adulterated because they present a significant or unreasonable risk of illness or injury (see 21 CFR 119.1). An ingredient may also be precluded from use in dietary supplements because it is an approved new drug that was not marketed as a food or dietary supplement before being approved as a drug, or because it was authorized for investigation as a new drug before being marketed as a food or dietary supplement, if substantial clinical

investigations have been instituted and the existence of the investigations has been made public (see section 201(ff)(3)(B) of the act. For example, FDA took action against dietary supplements containing the thyroid hormone tiratricol because it had been authorized for investigation as a new drug before it was marketed as a dietary supplement, and the existence of substantial clinical investigations of tiratricol had been made public (*United States* v. *Syntrax Innovations*, 149 F. Supp. 2d 880 (E.D.Mo. 2001)). Other ingredients may not fall within any of the dietary ingredient categories defined in section 201(ff)(1) of the act. For example, FDA issued a warning letter to a firm stating that its dietary supplement was adulterated because it contained human placenta, a substance which FDA concluded was not a dietary ingredient as defined in the act.

FDA intends to move beyond its current focus on products identified on the Internet and more closely scrutinize products in the marketplace. Initially these efforts will target products promoted for weight loss. This activity complements that of the FTC. In December 2003, the FTC identified eight claims about a product's ability to promote weight loss that a scientific panel convened by the commission staff had concluded were not ''scientifically feasible'' for nonprescription weight-loss products. The FTC published the claims (*http://www.ftc.gov/bcp/menu-health.htm* : under the ''business information'' section, Red Flag: ''A Reference Guide for Media on Bogus Weight Loss Claim Detection'' [PDF].) as a means to assist industry, the media, and consumers in identifying weight-loss claims that FTC has generally agreed to be false.